# What evidence exists for myofunctional therapy with prefabricated appliances? A systematic review with meta-analyses of randomised trials

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Abstract: Objective: To assess the treatment efficacy/efficiency with prefabricated myofunctional appliances (PMA) for children with malocclusion. Data sources: Nine databases searched without limitations till July 2019. Data selection: Randomised trials comparing PMAs to functional appliance treatment or no treatment. Data extraction: Study selection, data extraction and risk of bias assessment were done in duplicate. Data synthesis: Random-effects meta-analyses of mean differences (MDs) or relative risks (RRs) with their 95% confidence intervals (CIs) were conducted on seven publications (three published and one unpublished trials; 232 patients; 53% male; mean age 10.2 years). Compared to no treatment, one trial indicated that PMAs were somewhat effective in reducing overjet (MD -2.4; 95% CI -3.3 to -1.5), reducing overbite (MD -2.5; 95% CI -3.2 to -1.8), reducing mandibular crowding (RR 0.4; 95% CI 0.2-0.8) and establishing Class I canine relationship (RR = 2.3; 95% CI 1.1-4.9). However, compared to custom-made functional appliances, three trials indicated that PMAs were less effective in reducing the ANB angle (MD 0.9; 95% CI 0.5-1.4), increasing mandibular ramus length (MD -2.2; 95% CI -2.9 to -1.51), reducing overjet (MD 1.5; 95% CI 0.9-2.1), establishing a solid Class I molar relationship (RR 0.3; 95% CI 0.2-0.7), reducing the nasolabial angle (MD 5.8; 95% CI 0.8-10.8) and reducing facial convexity (MD -2.6; 95% CI -4.3 to -0.9). Finally, the quality of evidence was moderate to low due to risk of bias. Conclusions: PMAs are more effective in reducing overjet, overbite, mandibular crowding and establishing Class I canine relationship than no treatment. However, compared to custom-made functional appliances, PMAs are less effective in producing dental, skeletal or soft-tissue changes, even though they are less costly. Keywords: Class II malocclusion; evidence-based medicine; functional appliance; malocclusion; meta-analysis; myofunctional therapy; randomised trial; systematic review.

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## TITLE PAGE

# What evidence exists for myofunctional therapy with prefabricated appliances? A systematic review with meta-analyses of randomised trials

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## Abstract

**Objective**: To assess the treatment efficacy/efficiency with Prefabricated Myofunctional Appliances (PMA) for children with malocclusion.

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**Data selection:** Randomised trials comparing PMAs to functional appliance treatment or no treatment.

**Data extraction:** Study selection, data extraction, and risk of bias assessment were done in duplicate.

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**Conclusions**: PMAs are more effective in reducing overjet, overbite, mandibular crowding, establishing Class I canine relationship than no treatment. However, compared to custom-made functional appliances, PMAs are less effective in producing dental, skeletal, or soft-tissue changes, even though they were less costly.

**Keywords**: malocclusion, myofunctional therapy, functional appliance, Class II malocclusion, randomised trial, systematic review, meta-analysis, evidence-based medicine

# MANUSCRIPT

## 1. Introduction

### 1.1. Background

The interplay between soft tissue pressure from abnormal lip / tongue function, habits or respiratory problems and craniofacial development have been well documented and reported many decades ago (Moss and Rankow, 1968; Moss, 1997]. As a result, much attention has been paid to control the dentofacial growth by correcting oral dysfunction and establishing oral muscular balance (Owman-Moll and Ingervall, 1984).

Oral myofunctional therapy was introduced primarily by Rogers in the early 1900s (Cottingham, 1976), and was based on exercises aiming to establish proper oral function that would be compatible with good occlusion. A recent systematic review of however indicated that there is a lack of high-quality evidence in the existing literature regarding early orthodontic management and orofacial muscle training protocols on the correction of myofunctional and myoskeletal problems in the developing dentition (Koletsi et al., 2018). It is also important to note that Rogers considered myofunctional exercises as an aid in treatment and retention (Proffit and Mason, 1975) and not as a universal therapeutic approach for all orthodontic problems (Wishney et al., 2019).

Apart from orofacial muscle training exercises, myofunctional therapy has also including various myofunctional appliances, since the initial introduction of the oral screen in 1912 (Idris et al., 2018). Such myofunctional appliances include Prefabricated Myofunctional Appliances (PMA) like the oral shield (Cheney, 1958; Cheney, 1963), the double oral screen (Rossi et al., 1984), the Eruption Guidance Appliance (Bergersen, 1984), LM-Activator™, Myobrace®, Trainer for Kids™, and Occluso-Guide®. Common therapeutic protocols suggest that treatment with PMAs should be accompanied by myofunctional exercises as a part (Quadrelli et al., 2002; Tallgren et al., 1998). Some observational studies have shown that treatment with PMAs can influence oral muscle activity (Tallgren et al., 1998), reduce overjet (Tallgren et al., 1998; Quadrelli et al., 2002; Usumez et al., 2004), increase the SNB angle (Usumez et al., 2004), and increase facial height (Usumez et al., 2004). However, these studies presented several methodological limitations, including lack of an a priori registered protocol, lack of randomised treatment allocation, lack of allocation concealment, inappropriate control groups, lack of blinding, small-study effects, and reporting

biases (Papageorgiou et al., 2014; Papageorgiou et al., 2015a; Papageorgiou et al., 2015b; Koretsi et al., 2017; Papageorgiou et al., 2018; Papageorgiou et al., 2019a).

On the other hand, randomised clinical trials in recent years (Myrlund et al., 2015; Cirgic et al., 2016; Idris et al., 2018) indicate that initial findings from observational studies or marketing claims made by manufacturers of PMAs might not be true. A recent systematic review of randomised and non-randomised studies (Mohammed et al., 2019) found that PMAs were less effective in reducing overjet of patients with Class II malocclusion in the short-term compared to custom-made Activators, but this effect was diminished in the long-term. Also, PMAs were associated with reduced costs compared to custom-made Activators. However, the inclusion of non-randomised studies might have introduced bias (Papageorgiou et al., 2015a; Papageorgiou et al., 2015b). Additionally, the clinical relevance of dental, skeletal or soft-tissue effects of PMAs on growing children needs to be assessed both in terms of absolute efficacy compared just to physiological growth, as well as in terms of relative efficacy compared to functional appliances, which are considered the gold standard for early correction of mandibular retrusion (Koretsi et al., 2015; Batista et al., 2018).

### 1.2. Aim

Aim of this systematic review was to critically appraise existing evidence from randomised trials supporting the use of PMAs for the treatment of malocclusions in children compared to other interventions or untreated controls.

## 2. Materials and methods

### 2.1. Protocol and registration

The review's protocol was registered a priori (https://osf.io/v3pjr/) and all post hoc changes were noted (Appendix 1). This review was conducted and reported according to the Cochrane Handbook (Higgins and Green, 2011) and PRISMA statement (Liberati et al., 2009), respectively.

### 2.2. Eligibility criteria

According to the Participants-Intervention-Comparison-Outcome-Study design schema, included were parallel randomised clinical trials assessing the clinical performance of PMAs administered at healthy children of any sex, ethnicity, or malocclusion compared to functional appliances treatment or no treatment. No limitations concerning language, publication year, or publication status were applied. Excluded were non-randomised studies, case series/reports, animal studies, non-longitudinal studies, non-clinical studies, animal studies, and studies on children with systemic diseases, obstructive sleep apnoea, or receiving surgery.

### 2.3. Information sources and literature search

A total of nine electronic databases were searched systematically without any limitations from inception up to July 25th, 2019 (Appendix 2). In addition, Directory of Open Access Journals (DOAJ), Digital Dissertations (searched via UMI ProQuest), metaRegister of Controlled Trials, and Google Scholar were manually searched for additional trials. Finally, the reference/citation lists of eligible articles, as well as the reference lists of relevant reviews were checked for additional trials.

### 2.4. Study selection

Two authors (SNP, DK) screened the titles and/or abstracts of studies retrieved from the searches to identify those potentially meeting the inclusion criteria. The full text of potentially eligible trials was assessed by two authors (SNP, DK), while a third author (TE) was consulted for consensus in case of discrepancies.

### 2.5. Data collection and data items

Data collection was conducted by two authors (SNP, DK) using pre-defined forms covering: (i) study characteristics (design, clinical setting, country), (ii) patient characteristics (age, sex), (iii) malocclusion details, (iv) appliance used and any myofunctional training exercises, (v) status of treatment provider, (vi) patient compliance through treatment, (v) follow-up, and (vi) outcomes measured. Discrepancies between assessors were resolved like above, while data not provided in the article were calculated or requested from trialists (Appendix 1).

### 2.6. Risk of bias in individual trials

The risk of bias within included trials was assessed with the new Cochrane Risk Of Bias (ROB) 2.0 tool (Sterne et al., 2019) by two authors (SNP, DK) with the same way to resolve discrepancies.

### 2.7. Outcomes and data synthesis

As the outcome of early malocclusion treatment can be affected by patient characteristics (age, growth stage, malocclusion type/severity), the type of appliance, the patient's compliance, and the patient's individual growth potential, a random-effects model was deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning (Papageorgiou, 2014a). A restricted maximum likelihood random effects model was chosen a priori, based on recent guidance (Langan et al., 2019). Mean differences (MDs) for continuous outcomes and relative risks (RRs) for binary outcomes and their corresponding 95% confidence intervals (CIs) were chosen as effect sizes, while statistically significant RRs were translated into Numbers Needed to Treat (NNTs) to gauge their clinical relevance.

Between-study heterogeneity was assessed by inspecting the forest plots and by calculating the $\tau^2$ (absolute heterogeneity) and the $I^2$ statistics (relative heterogeneity). $I^2$ defines the proportion of total variability in the result explained by heterogeneity, but not chance. We considered arbitrarily $I^2$ over 75% to represent considerable heterogeneity, while also considering the heterogeneity's direction (localisation on the forest plot) and uncertainty intervals around heterogeneity estimates (Higgins et al., 2003). Ninety-five per cent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting (IntHout et al., 2016).

All analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX) by one author (SNP) and the dataset was openly provided (Papageorgiou et al., 2019b). All P values were two-sided with $\alpha$=5%.

### 2.8. Additional analyses, risk of bias across studies, and quality of evidence

Possible sources of heterogeneity were a priori planned to be sought through subgroup analyses and random-effects meta-regression in meta-analyses of at least 5 trials but could ultimately not be performed

(Appendix 1). Likewise, reporting biases were planned to be assessed in meta-analyses of at least 10 trials, but could ultimately not, due to the limited number of meta-analysed trials.

The overall quality of meta-evidence (i.e. the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, as very low, moderate, or high (Guyatt et al., 2011) and Summary of Findings tables were constructed using the improved format proposed by Carrasco-Labra et al. (2016). The minimal clinical important, large, and very large effects were defined as half, one, and two standard deviations of the pre-treatment measurement (for continuous outcomes) and RRs of 1.5, 2.0, and 5.0 (for binary outcomes) (Norman et al., 2003; Schünemann et al., 2009). The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Papageorgiou, 2014b) to assess heterogeneity, clinical relevance, and imprecision.

### 2.9. Sensitivity analyses

Robustness of the results was planned to be checked a priori with sensitivity analyses based on (i) inclusion/exclusion of trials with low risk of bias, (ii) improvement of the GRADE classification, and (iii) inclusion/exclusion of large trials (arbitrarily set as trials with at least 30 patients/group).

## 3. Results

### 3.1. Study selection

The electronic literature search yielded 187 results, while 5 more were identified manually (Fig 1). After removal of duplicates and screening of titles / abstracts, a total of 58 articles had their full text checked against the eligibility criteria. From these 5 journal papers, one doctoral dissertation, and one master's thesis, all published in English between 2010-2018, were considered eligible for inclusion. As three papers and the doctoral dissertation pertained to the same trial, a total of 4 unique trials were finally included in this review (Appendix 3). Three included studies were published as journal papers (one also as doctoral dissertation), while a still unpublished master thesis was provided upon request (Appendix 1).

### 3.2. Study characteristics

The characteristics of the 4 included trials are presented in Table 1. Three single-centre trials were conducted in orthodontic university clinics in Malaysia, Norway, or Syria, while a multi-centre trial was conducted in twelve general dental practices in Sweden. Three of the included trials compared PMAs to functional appliances, while the fourth trial compared PMAs to an untreated control group. These 4 trials included 124 patients treated with PMAs (range 16-57; average 31) and 108 patients treated with functional appliances or left untreated (range 17-40; average 27). Male patients constituted the 53% of all included patients (123/232) and had an overall mean age of 10.2 years. Patients included in the identified trials had mostly of Class II or Class I malocclusion with increased overjet, lip incompetence, overbite, crowding, and residual growth. The used PMAs included Myobrace® (Myofunctional Research Co, Australia), Trainer For Kids® (T4K or T4F, Myofunctional Research Co, Australia), or LM-Activator (LM-Instruments Oy, Finland), while the used functional appliances included Activator or Twin Block. Treatment was provided by 12 general dentists in the multi-centre trial from Sweden, while orthodontic specialists or orthodontic residents under supervision by orthodontic specialist treated patients in the remaining 3 trials. Assessment of patient compliance with the appliances was reported only in two instances: in one case directly through patient interview or notes and in one case indirectly through treatment discontinuation or failure. Patients were followed after appliance administration for 6 months (1 trial), 12 months (2 trials), or for an undescribed period until treatment success or failure, ranging from 3.6 to 40.3 months (1 trial). Two trials assessed outcomes from dental casts, two from lateral cephalograms, and one assessed clinical efficacy/efficiency aspects (including time and costs).

### 3.3. Risk of bias within studies

The risk of bias of included studies is given in detail in Appendix 4 and as summary in Table 2. The single trial comparing PMAs to no treatment presented only some concerns that pertained to possible baseline imbalances and the lack of an a priori registered protocol. The three trials comparing PMAs to functional appliance all presented high risk of bias for at least one domain. The single-centre trial from Malaysia was scored as presenting some concerns mainly due to the potential issues with the reported results and the documented analysis plan. The multi-centre trial from Sweden was scored negatively for issues in the randomisation process/baseline similarity, deviations from the intended intervention, lack of blind outcome

measurement, lack of an a priori registered protocol, and issues with the analysis/reporting of its results. Finally, the single-centre trial from Syria lacked blind outcome measurement and an a priori registered protocol.

### 3.4. Results of individual studies and data synthesis

The results of identified studies are presented separately for the comparison of PMA (LM-Activator®) versus no treatment (absolute efficacy) and separately for the comparison of various PMAs (Myobrace® or Trainer for Kids®) versus functional appliances (relative efficacy).

As far as absolute effects of PMAs are concerned, only one included trial provided evidence on their efficacy based on analysis of dental casts (Table 3). This indicated that a 12-month treatment with PMAs was successful in reducing overjet (MD: -2.4 mm; 95% CI: -3.3 to -1.5 mm; P<0.001) and overbite (MD: -2.5 mm; 95% CI: -1.8 mm; P<0.001) to a statistically and clinically relevant degree compared to no treatment. Additionally, treatment with PMAs was associated with greater percentage of patients (63% versus 30%) with Class I canine relationship (RR: 2.3; 95% CI: 1.1 to 4.9; P=0.03) compared to no treatment. Using the NNT, this can be interpreted as every 4$^{th}$ patient treated with PMA having a Class I canine relationship after 12 months that would not have if left untreated. Interestingly, no such significant benefit was seen for Class I molar relationship (P=0.16). Furthermore, treatment with PMAs was associated with less patients having crowding in the mandible (25% versus 60%) compared to no treatment (RR: 0.4; 95% CI: 0.2 to 0.8; P=0.02). According to the NNT, this meant that every 3$^{rd}$ PMA patient would avoid a mandibular crowding that would exist if the patient was left untreated.

As far as relative effects of PMAs against functional appliances are concerned, three trials were identified and could contribute to meta-analyses (Table 4). Treatment with PMAs was associated with 0.9° less ANB reduction (2 trials; 95% CI: 0.5 to 1.4°; P<0.001), 1.0° less SNB increase (2 trials; 95% CI: -1.6 to -0.4°; P=0.001), 1.5 mm less overjet reduction (95% CI: 0.9 to 2.1 mm; P<0.001), and 1.4 less ANS-Me increase (2 trials; 95% CI: -2.5 to -0.3°; P=0.01) compared to functional appliances. All meta-analyses were homogenous ($I^2$=0%) and the magnitude of the effects was mostly small to moderate (Fig 2-3). No significant differences could be found for changes in overbite, SNA, SN-ML, NL-ML, N-Me, 1s-NL, 1i-ML, and 1s-1i.

Apart from these meta-analyses, 37 more outcomes were assessed by single trials and are presented in Table 5, from which only results that are both statistically significant at 5% and potentially clinically relevant are discussed here. Treatment with PMAs was associated (compared to functional appliances) with smaller Condylion-Gonion distance (+0.5 and +2.7 mm, respectively; MD: -2.2 mm; 95% CI: -2.9 to -1.5 mm), smaller facial convexity angle (0 and +2.6°, respectively; MD: -2.6°; 95% CI: -4.3 to -0.9°), and smaller nasolabial angle (+1.8 and -4.0°, respectively; MD: 5.8°; 95% CI: 0.8 to 10.8°). Additionally, treatment with PMAs was associated with smaller percentage of patients with Class I molar relationship post-treatment (14% versus 45%; Fig 4) compared to functional appliances (RR: 0.3; 95% CI: 0.2 to 0.7). Using the NNT this means that for every 4$^{th}$ child treated with functional appliances instead of PMAs a Class I molar relationship is achieved, which would not be achieved if the child had been treated with PMAs. On the other hand, treatment with PMAs was associated with less visits (MD: -3.1 visits; 95% CI: -4.6 to -1.5 visits), less chair-time (MD: -78.0'; 95% CI: -113.5 to -42.5'), and less costs (MD: -574.0 €; 95% CI: -774.6 to -373.5 €) compared to functional appliances.

**3.5. Risk of bias across studies, quality of evidence, and additional analyses**

As only a couple of trials could be ultimately included in meta-analyses, no subgroup analyses, meta-regression analyses, or reporting bias analyses could be performed (Appendix 1).

The quality of existing evidence (i.e. the strength of clinical recommendations that can be formulated) was assessed with the GRADE approach (Table 6). Moderate quality of evidence supported the advantage of PMAs in terms of reduced costs and the disadvantages of PMAs in terms of worse occlusal (Class I molar relationship), skeletal (ANB angle and Cd-Go distance), and soft-tissue facial outcomes (facial convexity). This means that we can be fairly certain that the true effect is probably close to the estimated effect. On the other hand, low quality evidence supported the disadvantage of PMAs in terms of overjet reduction, which means that the true effect might be markedly different from the estimated effect and future studies might change this.

Sensitivity analyses according to bias or improvement of GRADE could likewise not be performed, since all trials presented some risk of bias and this was the reason for downgrading the quality of evidence.

Only one sensitivity analysis according to sample size could be performed in the meta-analysis of overjet reduction by including only the top trial of Fig 3, which gave consistent results.

## 4. Discussion

### 4.1 | Summary of evidence

The current systematic review summarizes evidence from 4 randomised trials on the clinical performance of PMAs for the treatment of children with (mostly Class II) malocclusion. The included trials moved on two major axes: comparison of PMAs to an untreated control group and comparison of PMAs to custom-made functional appliances.

As far as absolute effects of PMAs are concerned, some evidence about their efficacy was provided by a single trial from Norway (Myrlund et al., 2015). This indicated that PMAs provide clinically relevant dental effects consisting of overjet / overbite reduction, resolving of mandibular crowding and aid in establishing a Class I dental relationship at the canines. It seems that PMAs work mainly through protrusion / proclination of the lower anterior teeth and increase in the face height, which explains the corrections in overjet, overbite, crowding, and partial correction of the dental relationship only at the canine, but not the molar, while they do not significantly influence the mandibular morphology or the ANB angle. This is to some degree similar to the effects of treatment with some functional appliances. However, functional appliances are known to produce more pronounced changes in the posterior dentition and also produce significant changes in the mandibular condyles, ramus, corpus, as well as the sagittal maxilla-mandibular relationship (through the ANB angle) (Lund and Sandler, 1998; Koretsi et al., 2015; Kyburz et al., 2019). To this basis, it is important to frame any clinical recommendations about the use of PMAs for early treatment on malocclusion, on trials that directly assess the efficacy of PMAs relative to custom-made functional appliances, whose performance has been meticulously documented with ample evidence in the previous decades.

When the clinical performance of PMAs is compared to custom-made functional appliances a different picture is evident. Custom-made functional appliances have significantly more pronounced and clinically relevant effects than PMAs in terms of overjet reduction, ANB angle reduction, increase in mandibular ramus height, nasolabial angle reduction and reduction in facial convexity. Furthermore, they

are more successful in establishing a solid Class I relationship at the molars than PMAs (45% versus 14%). The more favourable dentofacial picture witnessed after the use of functional appliances may due to the fact that they are custom-made appliances, which allow a precise anterior mandibular repositioning determined by the construction wax bite. Moreover, they are rigid appliances made of acrylic material which is harder than that of many PMAs like the Trainer, specifically the starting appliance (i.e. the soft blue trainer). The high elasticity of the T4K® PMA has been reported as an important flaw noted and reported by parents (Idris et al., 2018); this elasticity made it difficult for children to keep their mandibles in a forward position (i.e. in an edge-to-edge relationship at the incisors).

On the other hand, the report from a single trial shown evidence that PMAs have a clear advantage over custom-made functional appliances in terms of reduced number of treatment visits, chair-time and overall treatment costs. This is straightforward, since PMAs are prefabricated and ready to be inserted in the mouth or can be easily mouldable in warm water.

There are several factors that can influence the results of early orthodontic treatment with either PMAs or functional appliances. For example, patient compliance with instructions to wear a removable appliance has been directly linked to the attained results throughout treatment with removable appliances (Al-Kurwi et al., 2017). Patient compliance in terms of appliance wear might be checked qualitatively through interviews with the patient and treatment notes or checked quantitatively by dedicated microsensors embedded in the appliance (Schott and Ludwig, 2014), which have shown that most patients do not comply with given instructions for appliance wear time. However, criticisms about the accuracy us such sensors have been expressed (Brierley et al., 2017) and the exact amount of minimum wear time needed to produce adequate remains debatable (Parekh et al., 2019). In the present review, only two of the included trials assessed in any way patient compliance with appliance wear, but only through indirect means and this cannot be taken formally into account.

Another factor that might influence the diagnosis, choice of treatment, and outcome of early orthodontic treatment is the training, knowledge, and expertise of the treatment provider (Akyalcin, 2019). Orthodontists and orthodontic residents are certainly trained to make better judgements about case complexity compared to general dentists, based on objective severity indices, which indicates that additional orthodontic education has an influence on the ability to arrive to better assessment of the case

and diagnosis (Heath et al., 2017). Another study (Marques et al., 2012) indicated that 50% of general dentists would fail the American Board of Orthodontists objective outcome evaluation of a case they considered best representative of their clinical practice. Interceptive treatment for posterior crossbites, managed by orthodontic specialists, has been reported to achieve higher success rate and lower treatment costs compared to treatment by general dentists (Sollenius et al., 2019). This agrees with a previous study from Finland, which indicated that general dentists with little orthodontic experience usually overrate their provided orthodontic care to their patients (Pietilä et al., 1998). In the present review one trial employed 12 general dentists for the early correction of Class II malocclusion with PMAs or functional appliances, but no information was given about systematic differences among the different trial centres or about the training, expertise, and calibration of the treatment providers, which might have influenced the trial's results.

### 4.2 | Strengths and limitations

This systematic review has several strengths, which include its a priori registered protocol (https://osf.io/v3pjr/), its comprehensive literature search, the sole inclusion of randomised trials (Papageorgiou et al., 2015a; Papageorgiou et al., 2015b), the use of modern analytic methods (Langan et al., 2019), application of the GRADE approach to assess the strength of provided recommendations (Guyatt et al., 2011), and the transparent provision of all data (Papageorgiou and Cobourne, 2018; Papageorgiou et al., 2019a). Finally, this review builds up on the recommendation from a previous systematic review of randomised and non-randomised studies (Mohammed et al., 2019) that reported that PMAs were less effective in reducing overjet but had significantly less treatment costs. The current review retains the superiority of functional appliances for overjet reduction, but extends this further to additional various dental, skeletal, and soft-tissue effects. Therefore, concrete differences in the efficacy and mode of treatment were seen between PMAs and functional appliances, which potentially undermine the suggested advantage of reduced costs for PMAs.

At the same time, some limitations also exist in the present review. First, both performed meta-analyses were based predominantly on small trials, which might affect their results (Cappelleri et al., 1996; Papageorgiou et al., 2014). Second, most trials assessed treatment effects after 6-12 months of treatment and not on the long term, when any catch-up growth effects might be observed. Finally, the small number

of trials that were ultimately included in the meta-analyses and their poor reporting of potential confounders precluded the conduct of analyses for subgroups, meta-regressions, and reporting bias that were initially planned (Appendix 1).

## 5. Conclusions

The current systematic review summarizes evidence from 4 randomised trials with 232 patients on the clinical performance of PMAs for the treatment of children with (mostly Class II) malocclusion. According to evidence of moderate to low quality, the following can be concluded:

- Compared to no treatment, PMAs seem to be effective in alleviating Class II malocclusion and mandibular crowding, which is mainly achieved through dentoalveolar effects (proclination of the lower incisors).
- Compared to orthodontic treatment with functional appliances, PMAs are significantly less effective in treating Class II malocclusion through dentoalveolar effects and have significantly less potential to modify skeletal growth or improve the facial profile, even though they associated with significantly lower treatment costs.
- Many of the claims made by manufacturers of PMAs about their clinical effect are unsubstantiated by up to date high quality evidence.
- There is currently no evidence for the relative performance of the different PMAs or for any patient- or treatment-related factors that might influence treatment outcome.

Therefore, even though PMAs might have some potentially beneficial characteristics, they cannot be suggested in an evidence-based manner as a regular early and solely treatment of malocclusion over conventional orthodontic treatment.

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## Figure Legends

**Fig 1.** PRISMA flowdiagram for the identification and selection of studies eligible in this review.

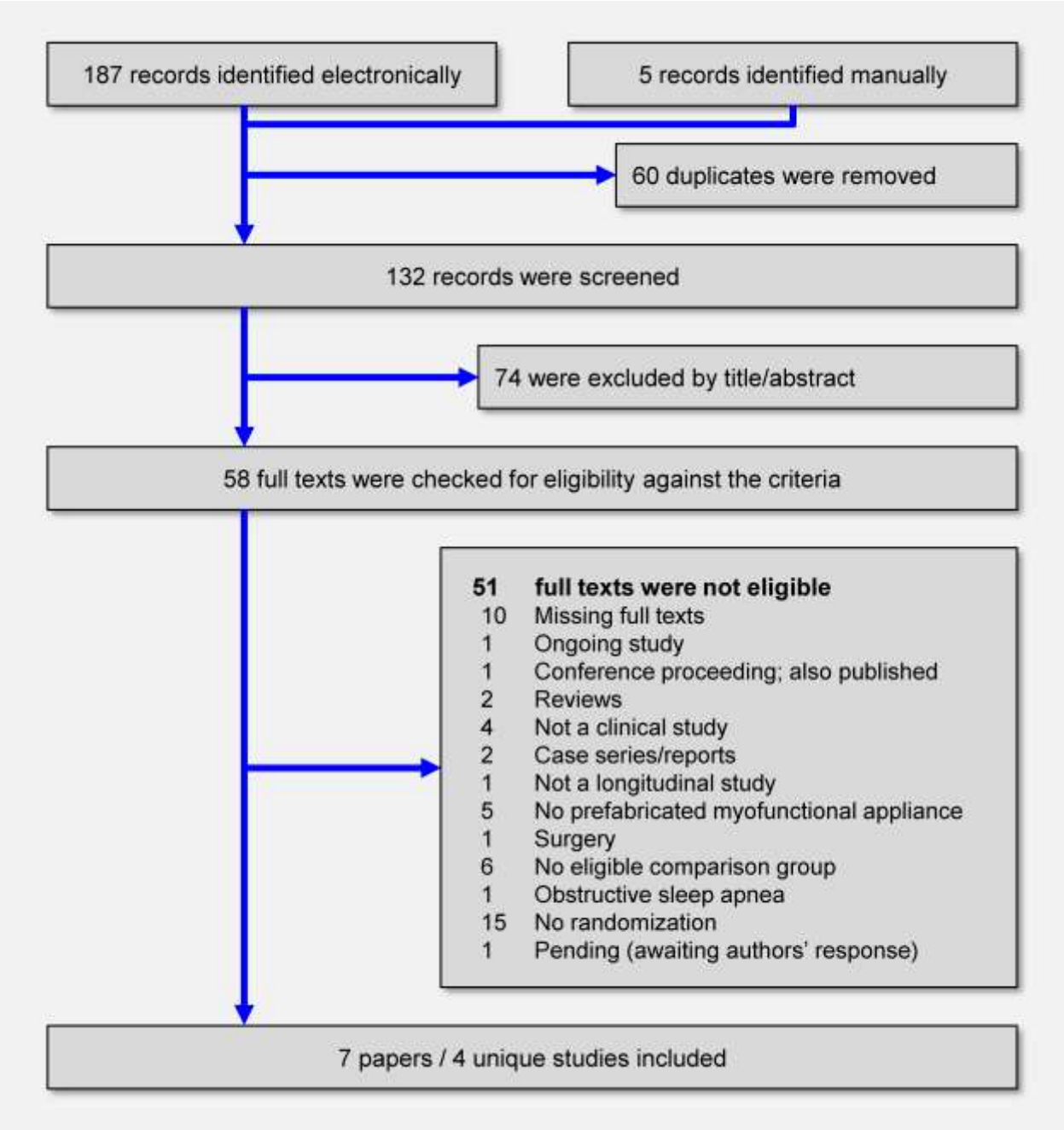


**Fig 2.** Contour-enhanced forest plot on the treatment effects of prefabricated myofunctional appliances versus functional appliances for change in ANB angle. CI, confidence interval; MD, mean difference; PMA, prefabricated myofunctional appliance; SD, standard deviation.

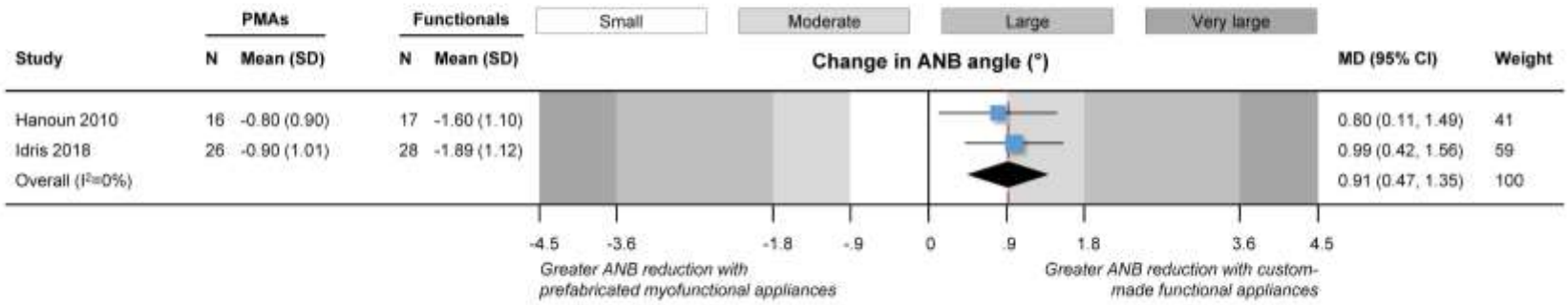


**Fig 3.** Contour-enhanced forest plot on the treatment effects of prefabricated myofunctional appliances versus functional appliances for change in overjet. CI, confidence interval; MD, mean difference; PMA, prefabricated myofunctional appliance; SD, standard deviation.

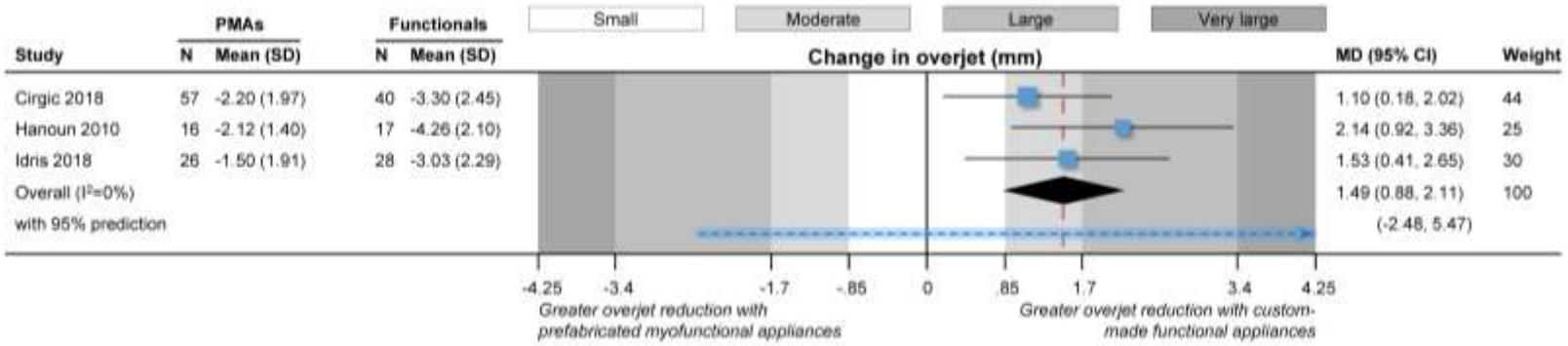
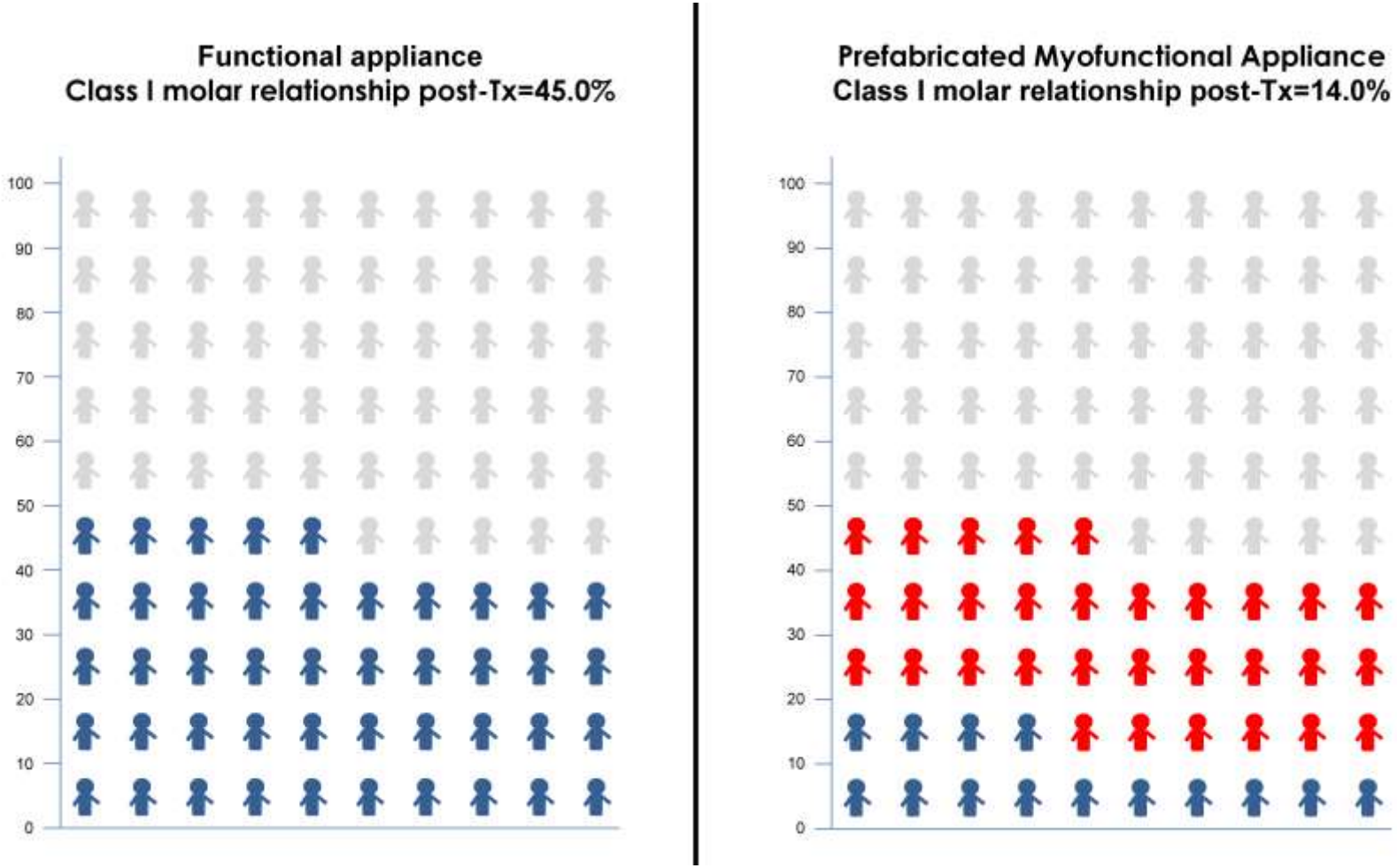


**Fig 4.** Expected relative frequency of people with Class I molar relationship post treatment with prefabricated myofunctional appliances versus functional appliances.



## TABLES

**Table 1.** Characteristics of included studies.

| Study | Design; setting; country* | Patients (M/F); age† | Malocclusion / Tx | Appliance | Provider | Compliance | FU | Outcome |
|---|---|---|---|---|---|---|---|---|
| Cirgic 2016; 2017a-c | RCT; Clinic; SWE | PMA: 57 (29/28); NR<br>RFA: 40 (24/16); NR<br>(overall age: 10.3) | Class II/1; OJ>6mm or lip incompetence | PMA: Myobrace®<br>RFA: Activator (mod) | GP | Through discontinuation / Tx failure | T1: 3.6-40.3 mos<br>T2: T1 + 12 mos | **Casts:** OB; OJ; sagMR<br>**Clinical:** Chairtime; costs; LiSe; Re-Tx need; Tx duration; Tx success; visits |
| Hanoun 2010 | RCT; Uni; MYS | PMA: 16 (9/7); 13.0<br>RFA: 17 (8/9); 13.2 | Class II/1; OJ≥7mm | PMA: T4F®<br>RFA: Twin Block | Ortho | NR | 6 mos | **LC:** various skeletal, dental, and soft-tissue parameters |
| Idris 2018 | RCT; Uni; SYR | PMA: 26 (14/12); 10.3<br>RFA: 28 (14/14); 10.6 | Class II/1; OJ>4mm; ANB>4°; Wits>2mm before/at growth spurt (HWR: PP2=, MP3=, S stages) | PMA: T4K® + exercises<br>RFA: Activator | Ortho | NR | 12 mos | **LC:** various skeletal, dental, and soft-tissue parameters |
| Myrlund 2015 | RCT; Uni; NOR | PMA: 25 (13/12); 7.7<br>CTR: 23 (12/11); 7.7 | Class I or II with:<br>(i) deepbite or (ii) OJ≥5mm or (iii) moderate crowding with OJ≥4mm | PMA: LM-Activator™<br>CTR: No Tx | Ortho | From FU interview and patient notes | 12 mos | **Casts:** OJ; OB; sagCR; sagMR; crowding‡ |

* countries given with their alpha-3 codes.
† patient age is given either mean.
‡ various skeletal, dental, and soft-tissue parameters were assessed from lateral cephalograms, but only in the PMA group, and are therefore not listed here.
CTR, control group; FU, follow-up; GP, general practitioner; HWR, hand wrist radiograph; LC, lateral cephalogram; LiSe, lip seal; M/F, male / female; mo, month; mod, modified; NR, not reported; OB, overbite; OJ, overjet; Ortho, orthodontist or orthodontic resident under supervision of orthodontist; PMA, prefabricated myofunctional appliance; RCT, randomised clinical trial; RFA, removable functional appliance; sagCR, sagittal canine relationship;
sagMR, sagittal molar relationship; Tx, treatment; Uni, university clinic; yr, year.

**Table 2.** Risk of bias of included trials.

| Nr | Reference | Randomisation process | Deviations from intended interventions | Mising outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|---|---|---|---|---|---|---|---|
| 1 | Cirgic 2016 | Some concerns | High | Low | High | High | High |
| 2 | Hanoun 2010 | Low | Low | Low | Low | Some concerns | Some concerns |
| 3 | Idris 2018 | Low | Low | Low | High | Some concerns | High |
| 4 | Myrlund 2015 | Low | Low | Low | Low | Some concerns | Some concerns |

**Table 3**. Outcomes assessed by the single included trial comparing prefabricated myofunctional appliances with no treatment. Results pertain to post-treatment values, since no increments were given and not other similar trials were included to calculate pre/post correlations.

| Nr | Trial | Outcome | Effect (95% CI) | P | ½ SD | Clinically relevant* |
|---|---|---|---|---|---|---|
| **1** | **Myrlund 2015** | **Overjet (mm)** | **MD:-2.40 (-3.27, -1.53)** | **<0.001** | **0.65** | **Yes** |
| **2** | **Myrlund 2015** | **Overbite (mm)** | **MD: -2.50 (-3.19, -1.81)** | **<0.001** | **0.70** | **Yes** |
| 3 | Myrlund 2015 | Class I molar relationship | RR:1.53 (0.85,2.76) | 0.16 | - | - |
| **4** | **Myrlund 2015** | **Class I canine relationship** | **RR:2.29 (1.08, 4.85)** | **0.03** | **-** | **Yes** |
| 5 | Myrlund 2015 | Crowding (maxilla) | RR:0.92 (0.55, 1.52) | 0.74 | - | - |
| **6** | **Myrlund 2015** | **Crowding (mandible)** | **RR:0.39 (0.18, 0.84)** | **0.02** | **-** | **Yes** |

CI, confidence interval; MD, mean difference; RR, relative risk; SD, standard deviation.

* potentially clinically relevant effect, judged as an effect that is statistically significant (P<0.05) and its effect is at least as big as the minimal clinical important effect: half a standard deviation (combined pre-treatment standard deviation of the two groups) or relative risk ≥ 1.50 (or ≤0.67).

**Table 4**. Results of the random-effects meta-analyses comparing prefabricated myofunctional appliances with functional appliances. Results pertain to treatment-related reductions (increments) and positive MD indicate smaller reductions with prefabricated myofunctional appliances.

| Outcome | Trials | MD (95% CI) | P | $I^2$ (95% CI) | $\tau^2$ (95%CI) | 95% PrI |
|---|---|---|---|---|---|---|
| Overjet | 3 | 1.50 (0.88, 2.11) | <0.001* | 0% (0%, 94%) | 0 (0, 4.53) | -2.48, 5.47 |
| Overbite | 2 | 0.64 (-0.08, 1.36) | 0.08 | 0% (0%, 98%) | 0 (0, 17.43) | - |
| SNA | 2 | -0.11 (-0.66, 0.44) | 0.70 | 0% (0%, 99%) | 0 (0, 24.98) | - |
| SNB | 2 | -1.04 (-1.64, -0.43) | 0.001* | 0% (0%, 98%) | 0 (0, 13.26) | - |
| ANB | 2 | 0.91 (0.48, 1.35) | <0.001* | 0% (0%, 99%) | 0 (0, 5.61) | - |
| SN-ML | 2 | 0.16 (-0.68, 1.01) | 0.70 | 0% (0%, 98%) | 0 (0, 22.24) | - |
| NL-ML | 2 | 0.53 (-0.39, 1.45) | 0.26 | 0% (0%, 98%) | 0 (0, 20.69) | - |
| N-Me | 2 | -1.73 (-4.91, 1.46) | 0.29 | 77% (0%, 100%) | 4.04 (0, 662.35) | - |
| ANS-Me | 2 | -1.39 (-2.50, -0.28) | 0.01* | 0% (0%, 98%) | 0 (0, 33.04) | - |
| 1s-NL | 2 | 0.44 (-0.63, 1.50) | 0.42 | 28% (0%, 99%) | 0.24 (0, 108.84) | - |
| 1i-ML | 2 | 0.09 (-1.47, 1.64) | 0.91 | 21% (0%, 99%) | 0.31 (0, 189.01) | - |
| 1s-1i | 2 | -0.84 (-3.38, 1.71) | 0.52 | 0% (0%, 99%) | 0 (0, 226.98) | - |

CI, confidence interval; MD, mean difference.

* statistically significant at the 5% level

**Table 5**. Treatment-related changes assessed by single included studies. Omitted are the outcome of ANB angle and overjet, since they are included in the meta-analyses of Table 4.

| Nr | Trial | Outcome | Effect (95% CI) | P | | ½ SD | Clinically relevant* |
|---|---|---|---|---|---|---|---|
| **1** | **Cirgic 2016** | **Class I molar relationship** | **RR:0.31 (0.15,0.65)** | **0.002** | | | **Yes** |
| **2** | **Cirgic 2016** | **Number of visits** | **MD:-3.05 (-4.60,-1.50)** | **<0.001** | | **2.05** | **Yes** |
| **3** | **Cirgic 2016** | **Emergency visits** | **MD:-0.60 (-0.90,-0.30)** | **<0.001** | | **0.45** | **Yes** |
| **4** | **Cirgic 2016** | **Chair time (min)** | **MD:-78.00 (-113.54,-42.46)** | **<0.001** | | **50.00** | **Yes** |
| **5** | **Cirgic 2016** | **Direct costs—material** | **MD:-152.00 (-175.57,-128.43)** | **<0.001** | | **37.50** | **Yes** |
| **6** | **Cirgic 2016** | **Direct costs—chair time** | **MD:-274.00 (-399.38,-148.62)** | **<0.001** | | **176.50** | **Yes** |
| **7** | **Cirgic 2016** | **Indirect costs** | **MD:-148.00 (-212.69,-83.31)** | **<0.001** | | **88.00** | **Yes** |
| **8** | **Cirgic 2016** | **Societal (total) costs** | **MD:-574.00 (-774.55,-373.45)** | **<0.001** | | **284.50** | **Yes** |
| 9 | Cirgic 2016 | Treatment failure (residual overjet>3mm) | RR:1.34 (0.95,1.88) | 0.09 | | | - |
| 10 | Cirgic 2016 | Retreatment need | RR:1.64 (0.69,3.90) | 0.27 | | | - |
| 11 | Cirgic 2016 | Treatment duration | MD:-2.64 (-5.77,0.49) | 0.10 | | | - |
| 12 | Hanoun 2010 | Ar-A (mm) | MD:0.16 (-0.57,0.89) | 0.67 | | 1.74 | - |
| 13 | Hanoun 2010 | Ar-B (mm) | MD:-0.57 (-2.10,0.96) | 0.46 | | 2.49 | - |
| 14 | Hanoun 2010 | Ar-Pog (mm) | MD:-0.64 (-2.27,0.99) | 0.44 | | 2.73 | - |
| 15 | Hanoun 2010 | Sella vertical-A (mm) | MD:-0.47 (-1.29,0.35) | 0.26 | | 2.02 | - |
| 16 | Hanoun 2010 | Sella vertical-Pog (mm) | MD:-1.84 (-3.31,-0.37) | 0.01 | | 4.25 | No |
| 17 | Hanoun 2010 | Lower/total anterior face height | MD:-0.01 (-0.02, 0) | 0.15 | | 0.02 | - |
| 18 | Hanoun 2010 | Sella vertical-1s (mm) | MD:-0.74 (-1.92,0.44) | 0.22 | | 3.25 | - |
| 19 | Hanoun 2010 | Sella vertical-1i (mm) | MD:-2.56 (-3.96,-1.16) | <0.001 | | 2.96 | No |
| 20 | Idris 2018 | N.A.Pog angle (°) | MD:-1.48 (-2.69,-0.27) | 0.02 | | 2.31 | No |
| 21 | Idris 2018 | S.N.Pog angle (°) | MD:-0.61 (-1.26,0.04) | 0.07 | | | - |
| 22 | Idris 2018 | FH-MP angle (°) | MD:1.01 (-0.12,2.14) | 0.08 | | | - |
| 23 | Idris 2018 | Y-axis angle (°) | MD:0.38 (-0.43,1.19) | 0.36 | | | - |
| 24 | Idris 2018 | Ar-Go-Me angle (°) | MD:-0.46 (-1.46,0.54) | 0.37 | | | - |
| 25 | Idris 2018 | Wits (mm) | MD:0.63 (-0.49,1.75) | 0.27 | | | - |
| 26 | Idris 2018 | SN-NL angle (°) | MD:-0.82 (-0.91,-0.74) | <0.001 | | 1.36 | No |
| 27 | Idris 2018 | Cd-Gn (mm) | MD:-1.44 (-3.76,0.88) | 0.22 | | | - |
| **28** | Idris 2018 | Go-Pog (mm) | MD:-1.27 (-2.74,0.20) | 0.09 | | | - |
| 29 | **Idris 2018** | **Cd-Go (mm)** | **MD:-2.18 (-2.85,-1.51)** | **<0.001** | | **2.18** | **Yes** |
| 30 | Idris 2018 | N-ANS (mm) | MD:-0.98 (-2.07,0.11) | 0.08 | | 2.29 | - |
| 31 | Idris 2018 | ANS-PNS (mm) | MD:-0.56 (-2.33,1.21) | 0.54 | | 2.15 | - |
| **32** | Idris 2018 | 1s-SN angle (°) | MD:0.80 (-1.99,3.59) | 0.57 | | 4.19 | - |
| **33** | **Idris 2018** | **Facial convexity angle (°)** | **MD:-2.59 (-4.27,-0.91)** | **0.003** | | **2.51** | **Yes** |
| 34 | **Idris 2018** | **Nasolabial angle (°)** | **MD:5.79 (0.82,10.76)** | **0.02** | | **5.17** | **Yes** |
| 35 | Idris 2018 | Mentolabial angle (°) | MD:-5.52 (-12.86,1.82) | 0.14 | | 7.72 | - |
| 36 | Idris 2018 | Ls-E line (mm) | MD:-0.30 (-1.08,0.48) | 0.45 | | 0.72 | - |
| 37 | Idris 2018 | Li-E line (mm) | MD:0.14 (-0.65,0.93) | 0.73 | | 0.80 | - |

CI, confidence interval; MD, mean difference; RR, relative risk; SD, standard deviation.

* potentially clinically relevant effect, judged as an effect that is statistically significant (P<0.05) and its effect is at least as big as the minimal clinical important effect: half a standard deviation (combined pre-treatment standard deviation of the two groups) or relative risk ≥ 1.50 (or ≤0.67).

**Table 6.** Summary of findings table according to the GRADE approach comparing prefabricated myofunctional appliances with functional appliances.

| | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | | | | |
|---|---|---|---|---|---|---|
| **Outcome [follow-up] Patients (trials)** | | **Functional appliance[a]** | **PMA** | **Difference with PMAs** | **Quality of the evidence (GRADE)[b]** | **What happens with PMAs** |
| Overjet reduction [6 mos –Tx end] 184 patients (3 trials) | - | 3.5 mm | - | 1.5 mm less (0.9 to 2.1 less) | ⊕⊕◯◯ low[c] due to bias | Probably lead to smaller reduction in overjet |
| Overbite reduction [6-12 mos] 87 patients (2 trials) | - | 1.0 mm | - | 0.6 mm less (1.4 less to 0.1 more) | ⊕⊕⊕◯ moderate[d] due to bias | Little to no difference in overbite reduction |
| Class I molar relationship [Tx end] 97 patients (1 trial) | RR 0.3 (0.15 to 0.65) | 45.0% | 14.0% (6.8%-29.3%) | 31.0% less (15.7% to 38.2% less) | ⊕⊕⊕◯ moderate[d,e] due to bias | Probably lead to less patients with Class I molar relationship |
| ANB reduction [6-12 mos] 87 patients (2 trials) | - | 3.2 mm | - | 1.3 mm less (0.6 to 2.0 less) | ⊕⊕⊕◯ moderate[d] due to bias | Probably lead to smaller reduction in ANB angle |
| Cd-Go increase [12 mos] 54 patients (1 trial) | - | 2.7 mos | - | 2.2 mm less (1.5 to 2.9 mm less) | ⊕⊕⊕◯ moderate[d] due to bias | Probably lead to smaller vertical development of the ramus |
| Facial convexity reduction [12 mos] 54 patients (1 trial) | - | 4.0 ° | - | 5.80 ° less (0.8 to 10.8 ° less) | ⊕⊕⊕◯ moderate[d] due to bias | Probably lead more convex faces |
| Total Tx costs [Tx end] 97 patients (1 trial) | - | 1548 € | - | 574.0 € less (373.5 to 774.6 € less) | ⊕⊕⊕◯ moderate[d,f] due to bias | Probably lead to higher treatment costs |

Interventions: Prefabricated myofunctional appliances (Myobrace®, T4F®, or T4K® with exercises) versus removable functional appliances (Activator, Twin Block) / Population: adolescent patients with any kind of malocclusion / Setting: private practices and university clinics (Malaysia, Sweden, Syria).

[a] Response in the control group is based on average response of included studies (random-effects meta-analysis).

[b] Starts from "high"

[c] Downgraded by two levels for bias due to multiple methodological issues.

[d] Downgraded by one level for bias due to methodological issues.

[e] Potentially large effect observed (RR<0.5), but no upgrading due to residual confounding.

[f] Potentially large effect observed (RR<0.5), but no upgrading due to residual confounding.

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; mo, month; PMA, prefabricated myofunctional appliance; RR, relative risk; Tx, treatment.

## SUPPLEMENTARY MATERIAL

**Appendix 1.** Additional review details and deviations from protocol.

**Communications with trialists**

- Dr. A.A. Hanoun was contacted on July 23rd, 2019 to request a full-text of his MSc thesis so it can be formally included in the review, since only a preview pdf could be acquired. The same was requested from the thesis supervisor Dr. N. Mokhtar, after Dr. Hanoun suggested so. The full text of the unpublished thesis was ultimately provided via e-mail on August 12th.
- Dr. E. Cirgic was contacted on July 25th, 2019 to request missing data (age, overbite changes, lip seal changes) and outcome data for either a common timepoint between groups or estimates adjusted for treatment duration (either as aggregate data or the trial's dataset). No response has yet been received.

**Additional methods**

- We back-calculated Pre/Post correlation for change in overjet in the PMA group (0.59) and the functional appliance group (0.40) from the Idris 2018 trial that provided both before-and-after data, as well as increments. These Pre/Post correlations were used to calculate overjet increments for the Cirgic 2016 trial.

**Deviations from protocol**

- We planned to calculate 95% random-effects predictions for all meta-analyses with ≥3 trials to aid in their interpretations, but only 2 meta-analyses with 2 trials each were ultimately performed.
- Several factors were planned to be assessed through subgroup analyses/meta-regressions in meta-analyses of at least 5 studies, but could ultimately not be conducted due to limited material/reporting: (i) subsets according to the patient characteristics (patient chronological age, skeletal age, sex, ethnicity, craniofacial configuration, masticatory activity, jaw, baseline malocclusion severity), (ii) subsets according to the different experimental interventions (different

experimental or control appliances), (iii) subset according to any co-interventions administered, (iv) subsets according to the inclusion of tooth extractions in the treatment plan, and (v) subsets to the treatment provider, including experience each system and status (orthodontist / general dentist).

- We planned to set a significance level of 10% for tests of between-studies or between-subgroups heterogeneity, but no such analyses were done due to limited studies being included.

**Appendix 2**. Literature search strategies for each database, including hits (as of July 25th, 2019).

| Database | Search | Limits | Hits |
|---|---|---|---|
| MEDLINE | "prefabricated myofunctional appliance" OR "prefabricated myofunctional appliances" OR "pre-fabricated myofunctional appliance" OR "pre-fabricated myofunctional appliances" OR "prefabricated functional appliance" OR "prefabricated functional appliances" OR "pre-fabricated functional appliance" OR "pre-fabricated functional appliances" OR "eruption guidance" OR "Myobrace" OR "Myo-brace" OR "LM-Activator" OR "Occlusoguide" OR " Occlus-o-Guide" OR (("Trainer" OR "T4K" OR "T4F") AND (myofunctional OR "myo-functional")) | | 86 |
| Embase | Same as MEDLINE | | 7 |
| CDSR | Same as MEDLINE | | 0 |
| DARE | Same as MEDLINE | | 0 |
| CENTRAL | Same as MEDLINE | | 0 |
| Scopus | TITLE-ABS-KEY ( "prefabricated myofunctional appliance" OR "prefabricated myofunctional appliances" OR "pre-fabricated myofunctional appliance" OR "pre-fabricated myofunctional appliances" OR "prefabricated functional appliance" OR "prefabricated functional appliances" OR "pre-fabricated functional appliance" OR "pre-fabricated functional appliances" OR "eruption guidance appliance" OR "Myobrace" OR "Myo-brace" OR "LM-Activator" OR "Occlusoguide" OR " Occlus-o-Guide" OR ( ( "Trainer" OR "T4K" OR "T4F" ) AND ( myofunctional OR "myo-functional" ) ) ) | Dentistry | 34 |
| WOK | Same as MEDLINE | DENTISTRY ORAL SURGERY MEDICINE | 28 |
| VHL | Same as MEDLINE | | 13 |
| WHO trials | myofunctional | | 19 |
| | | | |

CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Cochrane Database of Abstracts of Reviews of Effects; VHL, Virtual Health Library; WHO, World Health Organisation; WOK, Web of Knowledge.

**Appendix 3**. List of studies identified from the literature search and their inclusion/exclusion status, with reasons.

| Nr | Paper | Status |
|---|---|---|
| 1 | {JPRN-UMIN000011171} Pilot Study for ORAl myofunctional CLinical Evidence: elderly} 11/07/2013". Not recruiting. | Exclusion by title |
| 2 | {JPRN-UMIN000011488} Pilot Study for ORAl myofunctional CLinical Evidence: dementia} 14/08/2013". Not recruiting. | Exclusion by title |
| 3 | {JPRN-UMIN000014986} Randomized, multicenter, open, two-arm parallel group trial of Oral myofunctional training for Clinical evidence to dementia.} 29/08/2014". Not recruiting. | Exclusion by title |
| 4 | {JPRN-UMIN000016594} Oral myofunctional training trial for CLinical Evidence-Learning disabilities} 21/02/2015". Not recruiting. | Exclusion by title |
| 5 | {JPRN-UMIN000027547} Impact of self oral myofunctional theraphy in the patients of obstructive sleep apnea syndrome} 30/05/2017". Recruiting. | Exclusion by title |
| 6 | {JPRN-UMIN000035476} Myofunctional therapy effective for obstructive sleep apnea in elderly patients} 08/01/2019". Not recruiting. | Exclusion by title |
| 7 | {NCT00989209} Myofunctional Therapy in Facial Palsy} 02/10/2009". Not recruiting. | Exclusion by title |
| 8 | {NCT03061019} Comparison of Two Oral Myofunctional Reeducation Methods for Children With Obstructive Sleep Apnea} 14/02/2017". Recruiting. | Exclusion by title |
| 9 | {NCT03596606} Efficacy of Osteopathic Manual Therapy Combined With Myofunctional Exercise for Temporomandibular Chronic Disorders} 28/06/2018". Recruiting. | Exclusion by title |
| 10 | {RBR-4mt6yr} Effects of speech therapy on chewing of individuals who underwent surgery to correct an imbalance in facial pattern} 10/05/2016". Not recruiting. | Exclusion by title |
| 11 | Alves TP, Soares TR, Barreto SC, Fried H, Pereira GD, Maia LC, et al. Multidisciplinary approach for the treatment of extensive external cervical resorption after dental trauma. Oper Dent. 2013;38(4):349-57. | Exclusion by title |
| 12 | Baek SH, Park YH, Chung JH, Kim S, Choi JY. Orthodontic and orthopedic treatment for a growing patient with Tessier number 0 cleft. Korean J Orthod. 2018;48(2):113-24. | Exclusion by title |
| 13 | Braun C, Henneberger G, Racenberg E. [Techniques of continuous nerve block at the level of the wrist]. Ann Chir Main Memb Super. 1992;11(2):141-5. | Exclusion by title |
| 14 | Brin I, Ben-Bassat Y, Zilberman Y, Fuks A. Effect of trauma to the primary incisors on the alignment of their permanent successors in Israelis. Community Dent Oral Epidemiol. 1988;16(2):104-8. | Exclusion by title |
| 15 | Cheng AC, Tee-Khin N, Siew-Luen C, Lee H, Wee AG. The management of a severely resorbed edentulous maxilla using a bone graft and a CAD/CAM-guided immediately loaded definitive implant prosthesis: a clinical report. J Prosthet Dent. 2008;99(2):85-90. | Exclusion by title |
| 16 | Condo R, Perugia C, Bartolino M, Docimo R. Analysis of clinical efficacy of interceptive treatment of Class II division 2 malocclusion in a pair of twins through the use of two modified removable appliances. Oral Implantol (Rome). 2010;3(3):11-25. | Exclusion by title |
| 17 | Croft RS, Buschang PH, English JD, Meyer R. A cephalometric and tomographic evaluation of Herbst treatment in the mixed dentition. Am J Orthod Dentofacial Orthop. 1999;116(4):435-43. | Exclusion by title |
| 18 | Ebato A, Suzuki H, Sakamaki T, Ooguchi S, Chow CM, Komiyama O. Obstructive sleep apnea treatment with a twopiece mandibular advancement device with an elastic retention band in combination with orofacial myofunctional therapy: A case report. Sleep Science. 2019;12(1):57-60. | Exclusion by title |
| 19 | Epstein DD, Epstein PL, Cohen BI, Pagnillo MK. Comparison of the retentive properties of six prefabricated post overdenture attachment systems. J Prosthet Dent. 1999;82(5):579-84. | Exclusion by title |
| 20 | Flesch I. [Augmentation with antibiotic-impregnated spacers in sepsis revision surgery]. Unfallchirurg. 2015;118(10):844-50. | Exclusion by title |
| 21 | Freitas FCNd, Castro Ld, Bittencourt LP, Moraes APd, Bastos E. Aparelho Guia de Erupção na interceptação da sobremordida profunda: relato de caso. J bras ortodon ortop facial. 1999;4(19):29-34. | Exclusion by title |
| 22 | Guimaraes CH, Henriques J, Janson G, Moura WS. Stability of interceptive/corrective orthodontic treatment for tooth ankylosis and Class II mandibular deficiency: A case report with 10 years follow-up. Indian J Dent Res. 2015;26(3):315-9. | Exclusion by title |
| 23 | Hoffmann J, Cornelius CP, Groten M, Probster L, Pfannenberg C, Schwenzer N. Orbital reconstruction with individually copy-milled ceramic implants. Plast Reconstr Surg. 1998;101(3):604-12. | Exclusion by title |
| 24 | Hoffmann J, Cornelius CP, Groten M, Probster L, Schwenzer N. [Using individually designed ceramic implants for secondary reconstruction of the bony orbit]. Mund Kiefer Gesichtschir. 1998;2 Suppl 1:S98-101. | Exclusion by title |
| 25 | James AM, Williams CM, Haines TP. Effectiveness of footwear and foot orthoses for calcaneal apophysitis: a 12-month factorial randomised trial. Br J Sports Med. 2016;50(20):1268-75. | Exclusion by title |
| 26 | Jankulovska V, Chuchkova GK. Minimally invasive orthodontics in treatment of malocclusion class III: Case reports. Acta Stomatologica Croatica. 2016;50(1):95. | Exclusion by title |
| 27 | Janson G. Eruption guidance appliance effects - In response. American Journal of Orthodontics and Dentofacial Orthopedics. 2000;118(2):11A-A. | Exclusion by title |
| 28 | Katrana F, Kostopoulos E, Delia G, Lunel GG, Casoli V. Reanimation of thumb extension after upper extremity degloving injury treated with Integra. J Hand Surg Eur Vol. 2008;33(6):800-2. | Exclusion by title |
| 29 | Kim TW, Park JH. Eruption guidance in the mixed dentition: a case report. J Clin Pediatr Dent. 2008;32(4):331-9. | Exclusion by title |
| 30 | Kizi G, Barata R, Ribas D, Castaño Seiquer A, Ventura I. Early treatment of a class III malocclusion with the myobrace system: Clinical case. Annals of Medicine. 2018;50:S92-S3. | Exclusion by title |
| 31 | Krakowxzyk L, Maciejewski A, Szymczyk C, Grajek M, Stobiecka E, Poltorak S. Flap prefabrication using high-density porous polyethylene in an animal model - an experimental study. Med Sci Monit Basic Res. 2013;19:210-3. | Exclusion by title |
| 32 | Kupeyan HK, Shaffner M, Armstrong J. Definitive CAD/CAM-guided prosthesis for immediate loading of bone-grafted maxilla: a case report. Clin Implant Dent Relat Res. 2006;8(3):161-7. | Exclusion by title |
| 33 | Lagana G, Cozza P. Interceptive therapy with elastodontic appliance: case report. Ann Stomatol (Roma). 2010;1(3-4):22-8. | Exclusion by title |
| 34 | Ledingham WM, Wytch R, Goring CC, Mathieson AB, Wardlaw D. On immediate functional bracing of Colles' fracture. Injury. 1991;22(3):197-201. | Exclusion by title |
| 35 | Levrini L, Salone GS, Ramirez-Yanez GO. Efficacy of a Pre-Fabricated Myofunctional Appliance for the Treatment of Mild to Moderate Pediatric Obstructive Sleep Apnea: A Preliminary Report. J Clin Pediatr Dent. 2018;42(6):475-7. | Exclusion by title |
| 36 | Levrini L, Salone GS, Ramirez-Yanez GO. Pre-Fabricated Myofunctional Appliance for the Treatment of Mild to Moderate Pediatric Obstructive Sleep Apnea: A Preliminary Report. J Clin Pediatr Dent. 2018;42(3):236-9. | Exclusion by title |
| 37 | Luo J, Morrison DA, Hayes AJ, Bala A, Watts G. Single-Piece Titanium Plate Cranioplasty Reconstruction of Complex Defects. J Craniofac Surg. 2018;29(4):839-42. | Exclusion by title |
| 38 | Malivukovic A, Novakovic N, Lepic M, Minic L, Stepic N, Dordevic B, et al. Cranial reconstruction with prefabricated 3D implant after a gunshot injury: A case report. Vojnosanit Pregl. 2016;73(8):783-7. | Exclusion by title |
| 39 | McArdle BF. Using a fixed provisional prosthesis during post-extraction healing and implant placement. Compend Contin Educ Dent. 2006;27(3):179-84; quiz 85, 95. | Exclusion by title |
| 40 | Moir JS, Murali SR, Ashcroft GP, Wardlaw D, Matheson AB. A new functional brace for the treatment of Colles' fractures. Injury. 1995;26(9):587-93. | Exclusion by title |
| 41 | Morisaki I, Hashida S, Mihara J, Takagaki M, Sobue S. Complete root resorption of an upper central incisor due to ectopic eruption of canine in a deaf-mute child. J Osaka Univ Dent Sch. 1990;30:148-52. | Exclusion by title |
| 42 | Nergiz I, Arpak N, Bostanci H, Scorziello TM, Schmage P. Stability of loaded and unloaded implants with different surfaces. Int J Oral Maxillofac Implants. 2009;24(2):289-98. | Exclusion by title |
| 43 | Nkenke E, Agaimy A, Vairaktaris E, Lell M, von Wilmowsky C, Eitner S. Case History Report: Immediate Rehabilitation with a Prefabricated Fibula Flap Following Removal of a Locally Aggressive Maxillary Tumor. Int J Prosthodont. 2016;29(1):53-8. | Exclusion by title |
| 44 | O'Sullivan AD, Wicke D, Hengen TJ, Sieverding HL, Stone JJ. Life Cycle Assessment modelling of stormwater treatment systems. J Environ Manage. 2015;149:236-44. | Exclusion by title |
| 45 | Pompeia LE, Rossetti RM, Faria PR, Ortolani CLF, Junior KF. Tratamento de mordida aberta anterior com terapia miofuncional relato de caso. Ortho Sci, Orthod sci pract. 2017;10(37):75-81. | Exclusion by title |
| 46 | Ramirez-Yanez GO, Faria P. Early treatment of a Class II, division 2 malocclusion with the Trainer for Kids (T4K): a case report. J Clin Pediatr Dent. 2008;32(4):325-9. | Exclusion by title |
| 47 | Reich W, Seidel D, Bredehorn-Mayr T, Eckert AW. [Reconstruction of isolated orbital floor fractures with a prefabricated titanium mesh]. Klin Monbl Augenheilkd. 2014;231(3):246-55. | Exclusion by title |
| 48 | Romanos GE, May S, May D. Treatment concept of the edentulous mandible with prefabricated telescopic abutments and immediate functional loading. Int J Oral Maxillofac Implants. 2011;26(3):593-7. | Exclusion by title |
| 49 | Rustemeyer J, Dicke U. Prefabricated nerve conduits advance histomorphological and functional outcomes in nerve regeneration of the sciatic nerve of the rat. Int J Oral Maxillofac Surg. 2010;39(9):889-96. | Exclusion by title |
| 50 | Stern EB. Wrist extensor orthoses: dexterity and grip strength across four styles. Am J Occup Ther. 1991;45(1):42-9. | Exclusion by title |
| 51 | Vinci P, Gargiulo P. Poor compliance with ankle-foot-orthoses in Charcot-Marie-Tooth disease. Eur J Phys Rehabil Med. 2008;44(1):27-31. | Exclusion by title |
| 52 | Wahl G, Lang H. Deformation at the implant interface to prosthetic superstructure: an interferometric approach. Clin Oral Implants Res. 2004;15(2):233-8. | Exclusion by title |

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| 53 | Wang CH, Lee HE. [Stress distribution of prefabricated screw posts. Part II: Different designs and materials]. Gaoxiong Yi Xue Ke Xue Za Zhi. 1991;7(11):590-8. | Exclusion by title |
| 54 | Wilmes B, Vasudavan S, Drescher D. CAD-CAM-fabricated mini-implant insertion guides for the delivery of a distalization appliance in a single appointment. Am J Orthod Dentofacial Orthop. 2019;156(1):148-56. | Exclusion by title |
| 55 | Yukun L, Ke G, Jiaming S. Application of Nipple Retractor for Correction of Nipple Inversion: A 10-Year Experience. Aesthetic Plast Surg. 2016;40(5):707-15. | Exclusion by title |
| 56 | {RBR-5hhtrt} Efficiency of muscle training with visual support for swallowing in the elderly} 01/02/2018". Recruiting. | Exclusion by title |
| 57 | Grillo E, Curr F, Salvadori S, Vigan VM, Giannini L, Farronato G. Use of elastodontic appliances: A case report. Mondo Ortodontico. 2012;37(4):135-40. | Exclusion by title |
| 58 | Al-Sulaita N, White GE. Orthopedic approach in the treatment of a skeletal class II division 1 malocclusion with an anterior open bite. J Clin Pediatr Dent. 2005;29(3):205-10. | Exclusion by abstract |
| 59 | Barone S, Neri P, Paoli A, Razionale AV. Design and manufacturing of patient-specific orthodontic appliances by computer-aided engineering techniques. Proc Inst Mech Eng H. 2018;232(1):54-66. | Exclusion by abstract |
| 60 | Gujjar KR, Indushekar KR, Amith HV, Sharma SL. Modified distal shoe appliance--fabrication and clinical performance. J Dent Child (Chic). 2012;79(3):185-8. | Exclusion by abstract |
| 61 | Ierardo G, Luzzi V, Nardacci G, Vozza I, Polimeni A. Minimally invasive orthodontics: elastodontic therapy in a growing patient affected by Dentinogenesis Imperfecta. Ann Stomatol (Roma). 2017;8(1):34-8. | Exclusion by abstract |
| 62 | Kleinerman V, Bergersen EO. Preventive and interceptive orthodontics for the 5 to 12 year-old. Functional appliances: the Nite-Guide and Occlus-o-Guide techniques. Refuat Hapeh Vehashinayim (1993). 2011;28(2):8-18, 72. | Exclusion by abstract |
| 63 | Mahony D. Combining functional appliances in the straightwire system. J Clin Pediatr Dent. 2002;26(2):137-40. | Exclusion by abstract |
| 64 | Pae EK. Response of masticatory muscles to passive stretch stimulus - from perspectives of functional appliances. Korean J Orthod. 2012;42(2):64-72. | Exclusion by abstract |
| 65 | Pietila I, Pietila T, Pirttiniemi P, Varrela J, Alanen P. Orthodontists' views on indications for and timing of orthodontic treatment in Finnish public oral health care. Eur J Orthod. 2008;30(1):46-51. | Exclusion by abstract |
| 66 | Sood S, Kharbanda OP, Duggal R, Sood M, Gulati S. Muscle response during treatment of Class II Division 1 malocclusion with Forsus Fatigue Resistant Device. J Clin Pediatr Dent. 2011;35(3):331-8. | Exclusion by abstract |
| 67 | Tatara AM, Wong ME, Mikos AG. In vivo bioreactors for mandibular reconstruction. J Dent Res. 2014;93(12):1196-202. | Exclusion by abstract |
| 68 | Tripathi NB, Patil SN. Treatment of class II division 1 malocclusion with myofunctional trainer system in early mixed dentition period. J Contemp Dent Pract. 2011;12(6):497-500. | Exclusion by abstract |
| 69 | Wang X, Zhang JJ, Yuan FS, Wang Y, Li CH, Varrela JE, et al. [Three-dimensional analysis of the early correction of anterior crossbite using eruption guidance appliance]. Beijing Da Xue Xue Bao Yi Xue Ban. 2018;50(3):532-7. | Exclusion by abstract |
| 70 | Dainesi EA, Kawauchi MY, Roberto AFB. Correção precoce da sobremordida profunda com aparelho guia de erupção. Ortho Sci, Orthod sci pract. 2016;9(35):114-20. | Exclusion by abstract |
| 71 | Guarim JdA. Avaliação do crescimento mandibular em um respirador bucal após o tratamento com o uso dos aparelhos ortopédico pré-fabricados. Rev paul odontol. 2010;32(2):26-33. | Exclusion by abstract |
| 72 | Guimarães Junior CH, Pinto AS. Aparelho miofuncional para guia de erupção. J bras ortodon ortop facial. 2000;5(26):42-6. | Exclusion by abstract |
| 73 | Santos-Pinto PRd, Sanrtos-Pinto CCmd, Gandini LG, Santos-Pinto Ad, Pizol KDCE, Santos-Pinto Nd. Correção da má oclusão de Classe II com mordida profunda utilizando o aparelho guia de irrupção Oclus-o-guide. Rev clín ortodon Dental Press. 2009;8(3):91-100. | Exclusion by abstract |
| 74 | Methenitou S, Shein B, Ramanathan G, Bergersen EO. Prevention of overbite and overjet development in the 3 to 8 year old by controlled nighttime guidance of incisal eruption: a study of 43 individuals. J Pedod. 1990;14(4):219-30. | Exclusion by abstract |
| 75 | Pereira ACJ. Avaliação cefalométrica dos efeitos do Guia de Erupção no tratamento da má oclusão de Classe II, 1ª Divisão, após 10 meses, em jovens brasileiros, com idade média de 9 anos. 1995:151-. | Excluded; missing fulltext |
| 76 | Silva CCAd. Avaliação cefalométrica dos efeitos do aparelho Guia de Erupção no tratamento da má oclusão de classe II, divisão 1, após dois anos. 1997:175-. | Excluded; missing fulltext |
| 77 | Souza JEPd. Comparação da proporção de sucesso de três modalidades de tratamento ortodôntico: Frankel, Occlus-O-Guide e fixo, na correção da classe II. 2001:150-. | Excluded; missing fulltext |
| 78 | Bassigny F. [Early treatment of severe dento-maxillary dysharmony: eruption guidance of incisors and canines]. Rev Orthop Dento Faciale. 1990;24(2):191-218. | Excluded; missing fulltext |
| 79 | Bergersen EO. Preventive and interceptive orthodontics in the mixed dentition with the myofunctional eruption guidance appliance: correction of crowding, spacing, rotations, cross-bites, and TMJ. J Pedod. 1988;12(4):386-414. | Excluded; missing fulltext |
| 80 | Bergersen EO. Preventive and interceptive orthodontics in the mixed dentition with the myofunctional eruption guidance appliance: correction of overbite and overjet. J Pedod. 1988;12(3):292-324. | Excluded; missing fulltext |
| 81 | Bergersen EO. The eruption guidance myofunctional appliance in the consecutive treatment of malocclusion. Gen Dent. 1986;34(1):24-9. | Excluded; missing fulltext |
| 82 | Bergersen EO. The eruption guidance myofunctional appliance: case selection, timing, motivation, indications and contraindications in its use. Funct Orthod. 1985;2(1):17-21, 4-5, 8-33. | Excluded; missing fulltext |
| 83 | Bergersen EO. The eruption guidance myofunctional appliances: how it works, how to use it. Funct Orthod. 1984;1(3):28-9, 31-5. | Excluded; missing fulltext |
| 84 | Little RM. The effects of eruption guidance and serial extraction on the developing dentition. Pediatr Dent. 1987;9(1):65-70. | Excluded; missing fulltext |
| 85 | {NCT03863275} Analysis of Muscle Activity With Myofunctional Devices, Using Surface Electromyography} 22/02/2019". Not recruiting. | Excluded; ongoing study |
| 86 | Varrela J, Keski-Nisula K, Keski-Nisula L, Lehto R. Effects of orthodontic intervention with eruption guidance appliance in early mixed dentition. Journal of Dental Research. 2003;82:B374-B. | Excluded; conference proceeding |
| 87 | Wishney M, Darendeliler MA, Dalci O. Myofunctional therapy and prefabricated functional appliances: an overview of the history and evidence. Aust Dent J. 2019;64(2):135-44. | Excluded; review |
| 88 | Ricciardi C, Cagetti MG, Cattaneo S, Qing Hu Y, Strohmenger L. Interceptive orthodontic treatment with elastomeric appliances: Literature review and case reports. Dental Cadmos. 2017;85(3):146-54. | Excluded; review |
| 89 | Ahn ES, Kim AH, Shim YS, An SY. Oropharyngeal Airway Three-dimensional Changes after Treatment with Myobrace in Class II Retrognathic Children. Iran J Public Health. 2017;46(2):265-7. | Excluded; no clinical study |
| 90 | King RK. Eruption guidance appliance effects. Am J Orthod Dentofacial Orthop. 2000;118(2):11a. | Excluded; no clinical study |
| 91 | Migliaccio S, Aprile V, Zicari S, Grenci A. Eruption guidance appliance: a review. Eur J Paediatr Dent. 2014;15(2):163-6. | Excluded; no clinical study |
| 92 | Reukers HA, Bartzela T. [Orthodontics in general practice. 4. Eruption guidance appliances in orthodontics]. Ned Tijdschr Tandheelkd. 2008;115(3):133-6. | Excluded; no clinical study |
| 93 | Dinkova M. Vertical control of overbite in mixed dentition by trainer system. Journal of IMAB - Annual Proceeding (Scientific Papers). 2014;20(5):648-54. | Excluded; case report/series |
| 94 | Bergersen EO. Preventive eruption guidance in the 5-to-7-year-old. J Clin Orthod. 1995;29(6):382-95. | Excluded; case report/series |
| 95 | {ChiCTR1800016467} A study about the periodontal condition of patients with mouth breathing after wearing myofunctional appliance} 2018-06-02". Recruiting. | Excluded; no longitudinal study |
| 96 | {ISRCTN20400513} The effectiveness of an orthodontic brace for a receding chin} 12/06/2013". Not recruiting. | Excluded; no myofunctional appliance |
| 97 | {JPRN-UMIN000032179} Effect of myofunctional therapy on subjects with lip incompetence - Multimodality analysis} 10/04/2018". Recruiting. | Excluded; no myofunctional appliance |
| 98 | {JPRN-UMIN000036005} Effect of muscular function therapy on tongue thrust- Investigation by multi modality analysis} 25/02/2019". Recruiting. | Excluded; no myofunctional appliance |
| 99 | {RBR-728mj2} Evaluation of the development of chewing, breathing, speech and swallowing functions in children with sucking habit} 22/11/2018". Not recruiting. | Excluded; no myofunctional appliance |

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| 100 | Nilsson JL, Shu X, Magnusson BH, Burt IA. A comparative study with Twin-block and Activator-Headgear appliances. Swedish Dental Journal. 2016;40(1):79-90. | Excluded; no myofunctional appliance |
| 101 | {NCT01562249} Rehabilitative Management of Mastication} 21/03/2012". Not recruiting. | Excluded; surgery |
| 102 | Condo R, Costacurta M, Perugia C, Docimo R. Atypical deglutition: diagnosis and interceptive treatment. A clinical study. European Journal of Paediatric Dentistry. 2012;13(3):209-14. | Excluded; no eligible controls |
| 103 | Freitas CMd, Freitas RR, Silva JRC. Uso do Sistema Trainer no centro de especialidades odontológicas (CEO) de Ortodontia da ASCES (Caruaru-PE). Ortho Sci, Orthod sci pract. 2012;5(20):491-7. | Excluded; no eligible controls |
| 104 | Oliveira Júnior EBd, Nouer PRA, Almeida RCd, Nogueira FF, Ramirez-Yañez GO. Avaliação cefalométrica de pacientes submetidos ao tratamento com posicionadores tipo Trainer - T4k. J bras ortodon ortop facial. 2005;10(56):179-85. | Excluded; no eligible controls |
| 105 | Quintella C, Martins DR, Janson G. Avaliação da influência do guia de erupção occlus-o-guide, nos incisivos superiores e inferiores, com rizogênese incompleta. Ortodontia. 2004;37(1):50-6. | Excluded; no eligible controls |
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SD, standard deviation.

**Appendix 4**. Detailed assessment of included randomised trials with the RoB 2.0 tool (supplement to Table 2).

| Domain | Reference | Cirgic 2015 | Hanoun 2010 | Idris 2018 | Myrlund 2015 |
|---|---|---|---|---|---|
| 1. Randomisation process | 1.1 | PY | Y | Y | Y |
| | 1.2 | PY | Y | Y | Y |
| | 1.3 | PY | N | N | PN |
| | Judgement | Some concerns | Low | Low | Low |
| 2. Deviations from intended interventions | 2.1 | Y | Y | Y | Y |
| | 2.2 | Y | Y | Y | Y |
| | 2.3 | PY | PN | PN | PN |
| | 2.4 | PY | NA | NA | NA |
| | 2.5 | PN | NA | NA | NA |
| | 2.6 | PY | Y | Y | Y |
| | 2.7 | NA | NA | NA | NA |
| | Judgement | High | Low | Low | Low |
| 3. Mising outcome data | 3.1 | Y | PN | PY | PY |
| | 3.2 | NA | PY | NA | NA |
| | 3.3 | NA | NA | NA | NA |
| | 3.4 | NA | NA | NA | NA |
| | Judgement | Low | Low | Low | Low |
| 4. Measurement of the outcome | 4.1 | N | N | N | N |
| | 4.2 | PN | N | N | PN |
| | 4.3 | Y | N | PY | N |
| | 4.4 | PY | NA | PY | NA |
| | 4.5 | PY | NA | NI | NA |
| | Judgement | High | Low | High | Low |
| 5. Selection of the reported result | 5.1 | NI | NI | NI | NI |
| | 5.2 | PY | PN | N | N |
| | 5.3 | Y | PN | N | N |
| | Judgement | High | Some concerns | Some concerns | Some concerns |
| Overall | Judgement | High | Some concerns | High | Some concerns |